Original Research Article

Spectrum of histomorphological patterns of adrenal tumors: A one year study at Gandhi Hospital, Hyderabad - A tertiary referral centre

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Abstract

Introduction: Adrenal gland is a bipartite endocrine gland divided into cortex and medulla. As their developments are different, a wide range of tumours are encountered. We have presented here adrenal tumors of varied histomorphology, in one year study from August 2013 to July 2014, at Gandhi Hospital, Hyderabad.

Aim and objectives: To study the spectrum of adrenal tumors diagnosed at Gandhi hospital for over a period of one year, correlation with clinical features and an overview of the pit falls encountered.

Materials and methods: All the adrenal gland specimens submitted to the Department of Pathology, Gandhi Hospital, Hyderabad, from August 2013 to July 2014 were included in the study. These specimens were subjected to routine processing and ancillary techniques were used to arrive at final diagnosis.

Results: A total of 8 cases were encountered in the present study. Majority of the tumors were seen in the age group of 20-40 years with female preponderance and only 37.5% were detected co-incidentally on imaging. Pheochromocytoma was the commonest tumor encountered (50%).
Conclusion: We encountered a total of 8 cases of Adrenal gland tumours, including almost one from each category of the WHO classification. Majority of the tumors were seen in the age group of 20-40 years with female preponderance. Pheochromocytoma was the commonest tumor encountered (50%).

Key words

Adrenal gland tumors, Cortical tumors, Medullary tumors, IHC.

Introduction

Adrenal gland is a bipartite endocrine gland divided into cortex and medulla having different development, structure and function. Cortex is derived from mesoderm and produces steroid hormones. Medulla is of neural crest origin and produces catecholamines. Large sized tumors, functional tumors and malignant tumors have poor prognosis and pose diagnostic challenges. In the present study, we have reported 8 cases of adrenal gland tumors within a span of just one year. Interestingly, the presentation of the cases varied clinically and morphologically.

Materials and methods

The present study was a cross sectional study carried out in the Department of Pathology, Gandhi Hospital, Hyderabad, a Tertiary Referral Centre. All the adrenal gland specimens received during the period from August 2013 to July 2014 were included in the study. An elaborate relevant clinical history was elicited including the indications for the surgery. Results of all the relevant biochemical investigations, hormonal assays and radiological findings were recorded. All the specimens were fixed in 10% formalin for 24 hours. Each specimen was grossed thoroughly. The weight, size, capsule, cut surface and other changes were recorded in the grossing format and analyzed. Representative bits were taken, subjected to routine processing, embedded in paraffin, stained with routine Hematoxylin and Eosin stain along with special stains like Perl's prussian blue stain, PAS, Bleaching ($KmnO_4$ method) where ever necessary. Immunohistochemistry panel used included α Inhibin, Melan A, Ki67, p53, Chromogranin, Synaptophysin, S-100 and HMB45 markers. The histopathological sections were studied and the microscopic findings were correlated with the clinical data. The findings of H and E sections, special stains and Immunohistochemistry were compiled to arrive at a final diagnosis. The results of the study were compared with the literature (**Figures – 1 to 6**).

Results

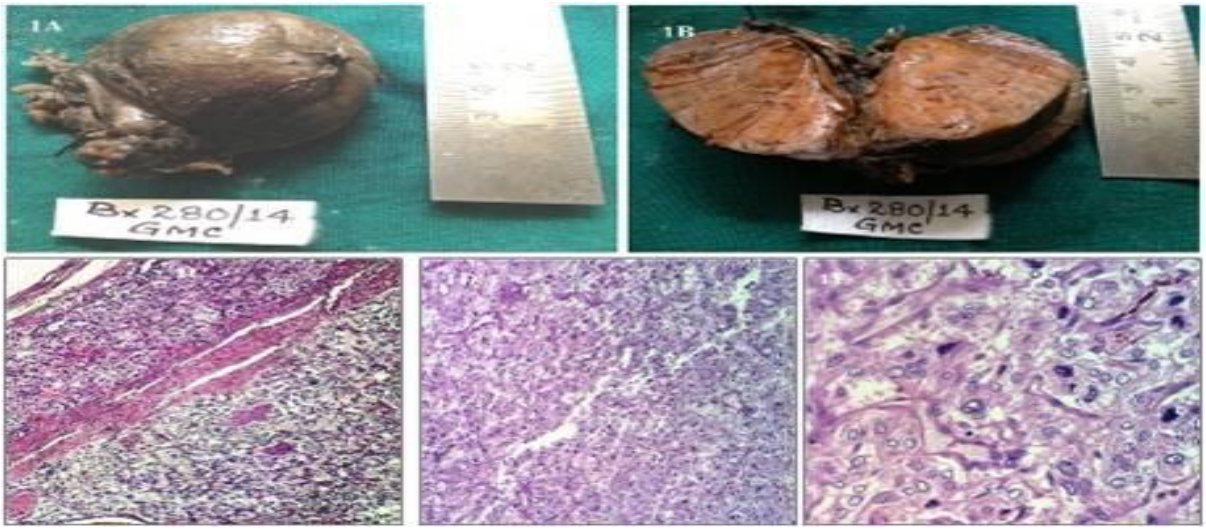
A total of 4333 specimens were submitted to the pathology department, during the above mentioned period, out of which 8 were adrenal masses, constituting approximately 0.2%. All the 8 cases were included in the study. Majority of the cases (75%) were between 20-40 years of age. 12.5% each belonged to the age groups of less than 20 years and more than 40 years. Mean age of the cases was 36 years; male to female ratio was 3: 5, constituting 37.5% male and 62.5% female. Majority of the cases were symptomatic, presenting with hypertension (2 cases), virilisation (2 cases) and 1 case with acute abdomen. Ultrasonography of all the cases showed suprarenal mass. After compiling the findings of routine H and E, special stains and IHC, final diagnosis of the lesions was arrived at. All the lesions were neoplastic. The tumors included Pheochromocytoma (4), Adrenal adenoma (2), Myelolipoma (1) and Ganglioneuroma (1). 2 cases of pheochromocytoma had positive results for vanillyl mandelic acid and metanephrine in urine. One case of pheochromocytoma, presented as a surgical emergency with intra-abdominal hemorrhage, with brownish black pigmented huge mass. Sections showed brownish black

coloured pigment. Initially on routine H and E we entertained a differential diagnosis of Pigmented Pheochromocytoma. For confirmation we had done bleaching and perl's prussian blue staining. The pigment did not disappear on bleaching and perl's stain showed positivity for the pigment. Hence, it was labelled as hemorrhage into the tumor Pheochromocytoma. 2 cases of pheochromocytoma presented with hypertension, refractory to conventional treatment. On imaging adrenal mass was detected in both the cases and adrenalectomy was done. 1 pheochromocytoma was an incidentaloma. Both cases of adrenal adenoma, presented with virilisation one showed atypical features on histopathology. The remaining 2 cases were incidentalomas, one case being myelolipoma and other case a ganglioneuroma (**Table – 1**).

Table – 1: Immunohistochemistry.

Neoplasm	**Inhibin**	**Melan A**	**Ki 67**	**S 100 Protein**	**Chromo granin**	**p53**	**HMB45**
Pheochromocytoma			-	+	+		
Haemorrhage into Pheochromocytoma	-	-	-	+	+		-
Adrenalcortical Adenoma	+	+	1%	-	-	-	
Adrenalcortical Adenoma with Atypical features	+	+	2%	-	-	-	

Figure - 1A: Gross photograph of Pheochromocytoma.
Figure - 1B: Cut section shows mahagony brown color.
Figures - 1C, 1D, and 1E: H and E sections on 4X, 10X and 40X views revealing classical zell ballen pattern of the tumor, respectively.



Discussion

WHO Histological Classification of Tumors of the Adrenal Gland
I.Adrenal Cortical Tumors
Adrenal Cortical Carcinoma
Adrenal Cortical Adenoma
II.Adrenal Medullary Tumors
Malignant Pheochromocytoma
Benign Pheochromocytoma/ Paraganglioma

Mixed Tumors
Composite Pheochromocytoma
III.Extra Adrenal Paraganglioma
IV .Other Adrenal Tumors
Adenomatoid tumour
Sex-cord stromal tumour
Soft tissue and Germ cell tumours
Teratoma
Myelolipoma
Schwannoma
Ganglioneuroma
Angiosarcoma
V. Secondary Tumors.

Figures - 1F, 1G, and 1H: 4X, 10X and 40X views of Positive IHC for Chromogranin in tumor cells.
Figures - 1I, and 1J: 10X and 40X views of Positive IHC for S100 protein in the sustentacular cells.

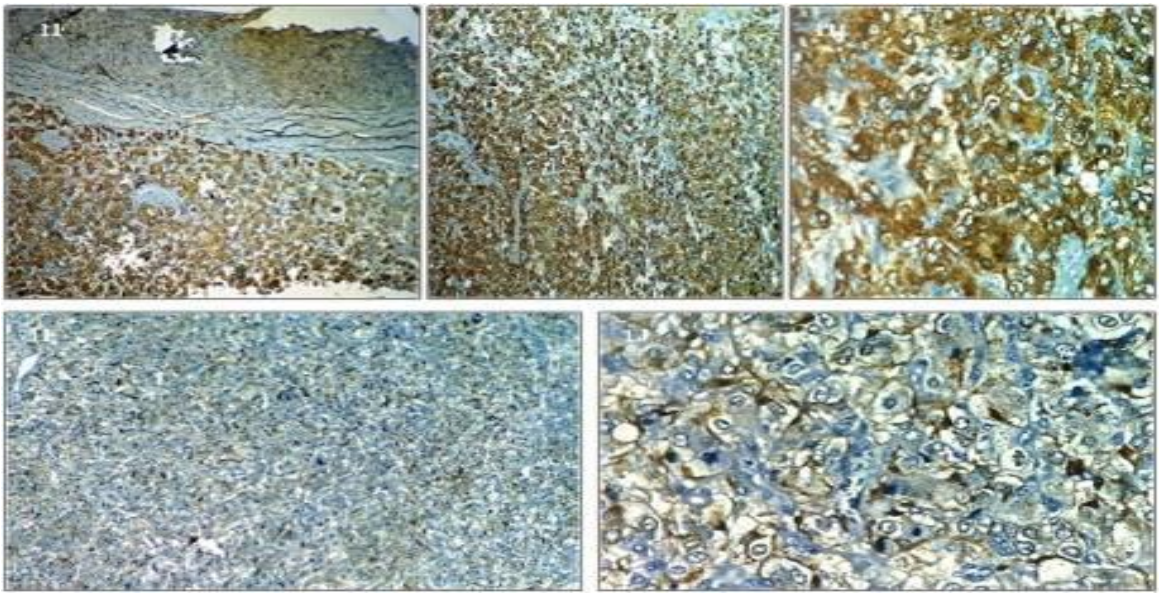


Figure - 2A: Gross photograph of Hemorrhage into Pheochromocytoma.
Figures - 2B, and 2C: Cut section of the same with extensive areas of hemorrhages.
Figures - 2D, and 2E: H and E sections on 4X, 40X views revealing extensive areas of hemorrhages.
Figure - 2F: H and E section on 40X view showing collections of histiocytes.
Figure - 2G: Special stain – Perl's Positive for bluish pigment hemosiderin.

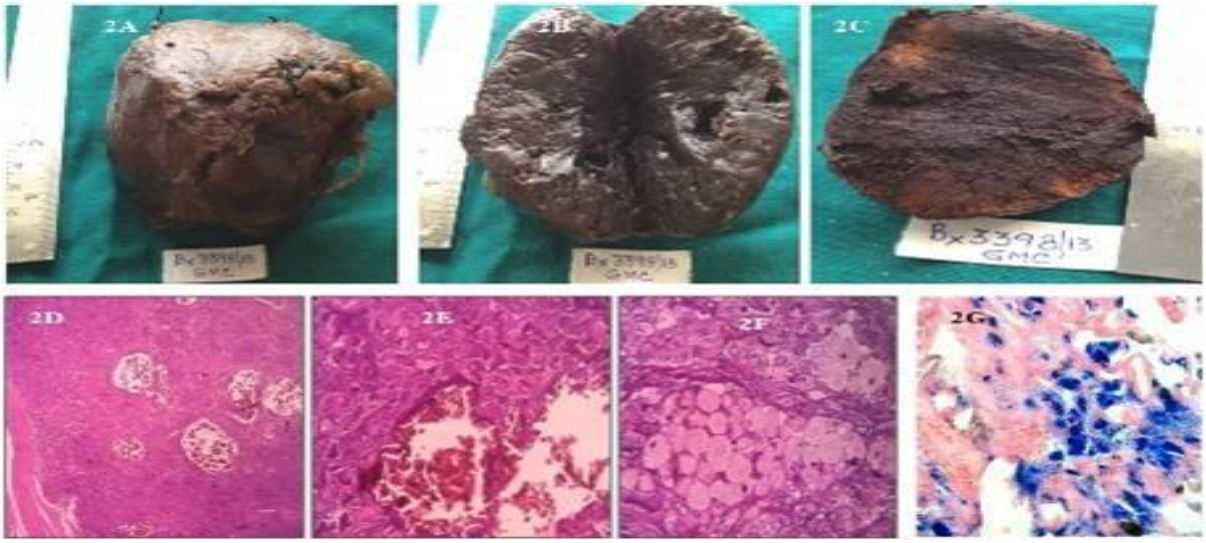
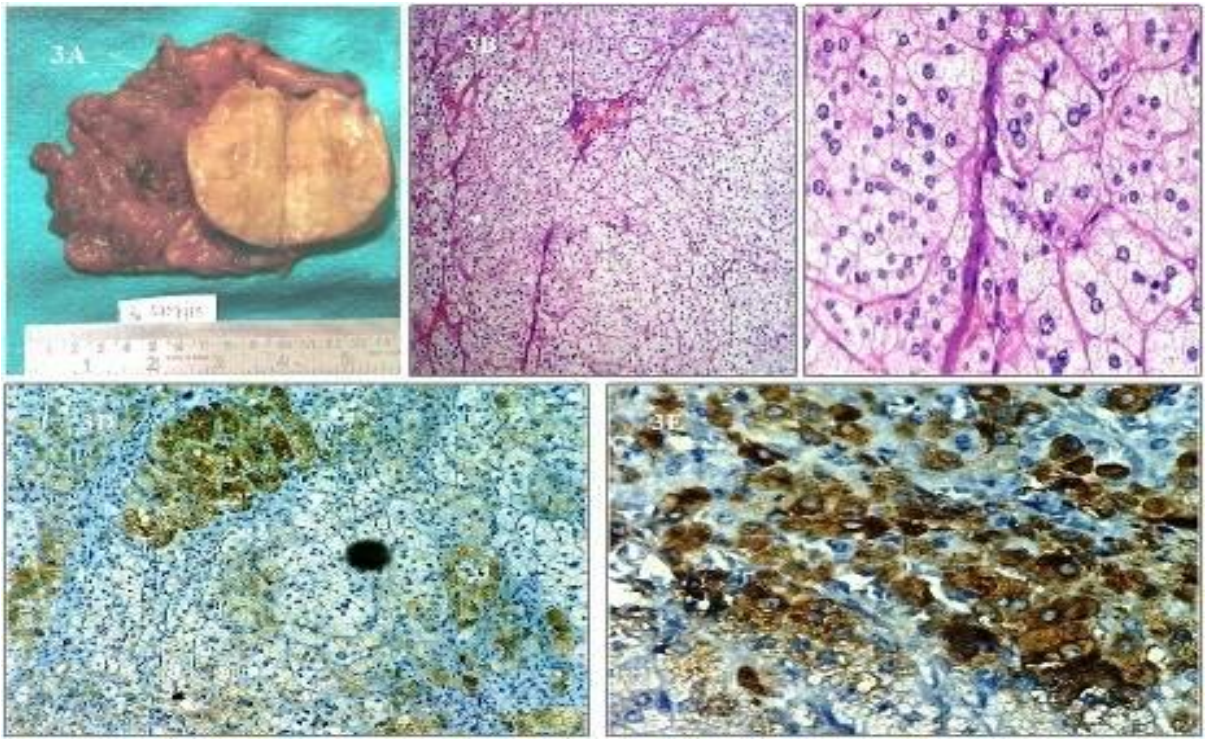


Figure - 3A: Cut section of Adrenal cortical adenoma showing uniform yellowish tint.
Figures - 3B, and 3C: H and E sections on 10X and 40X views showing clear cells in lobules and sheets.
Figures - 3D, and 3E: IHC confirmation by marker inhibin alpha on 10X and 40X views.



Figures - 4A, and 4B: Showing gross pictures of adrenal gland tumor with atypical features, on cut section more of grey white than yellowish areas are noted.
Figures - 4C, and 4D: H and E sections with focal nuclear pleomorphism, and multi nucleation.
Figures - 4E, and 4F: IHC confirmation by inhibin alpha in tumour cells.

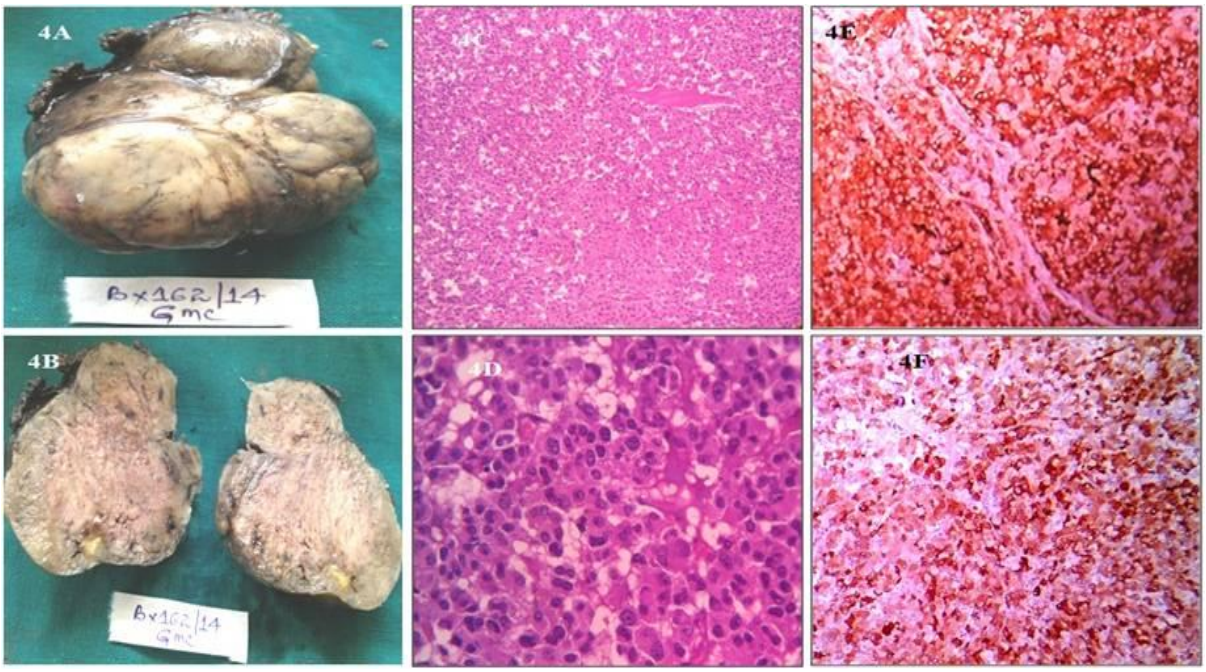


Figure - 5A: Multiple grey white to grey brown bits of enucleated myelolipoma of adenal gland.
Figures - 5B, and 5C: H and E sections high lighting both the lipomatous and hemopoietic areas on 4X and 10X views.
Figure - 5D: H and E on 40X view high lighting hematopioietic elements.

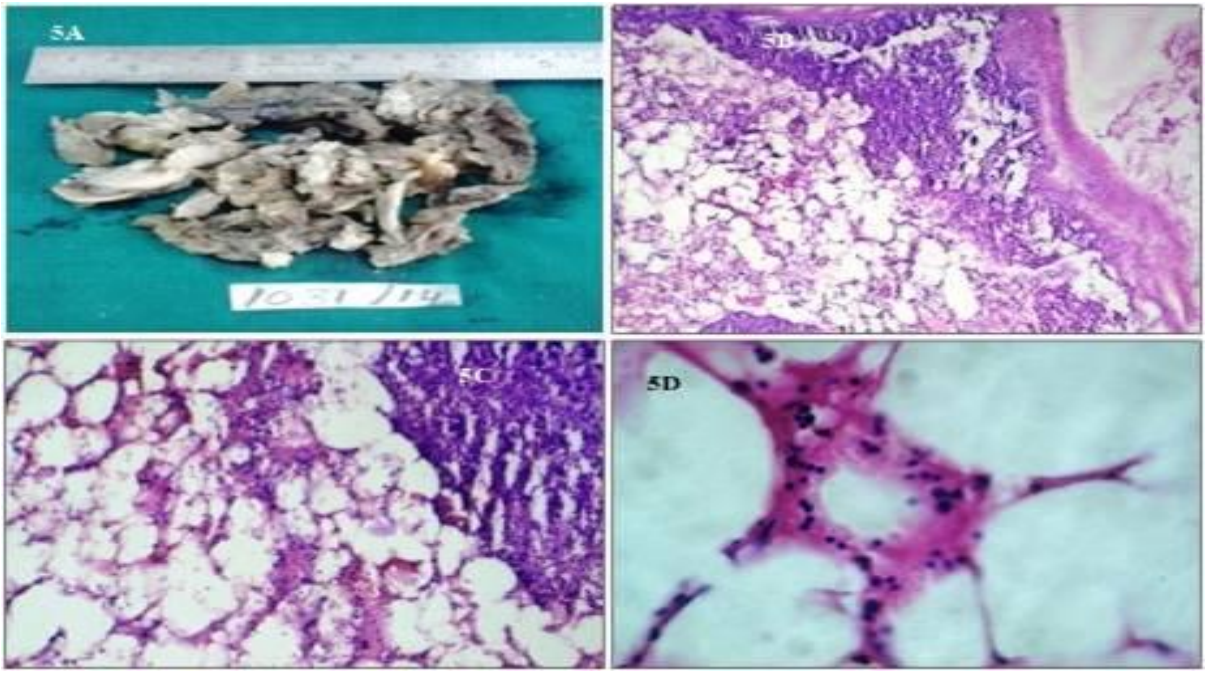
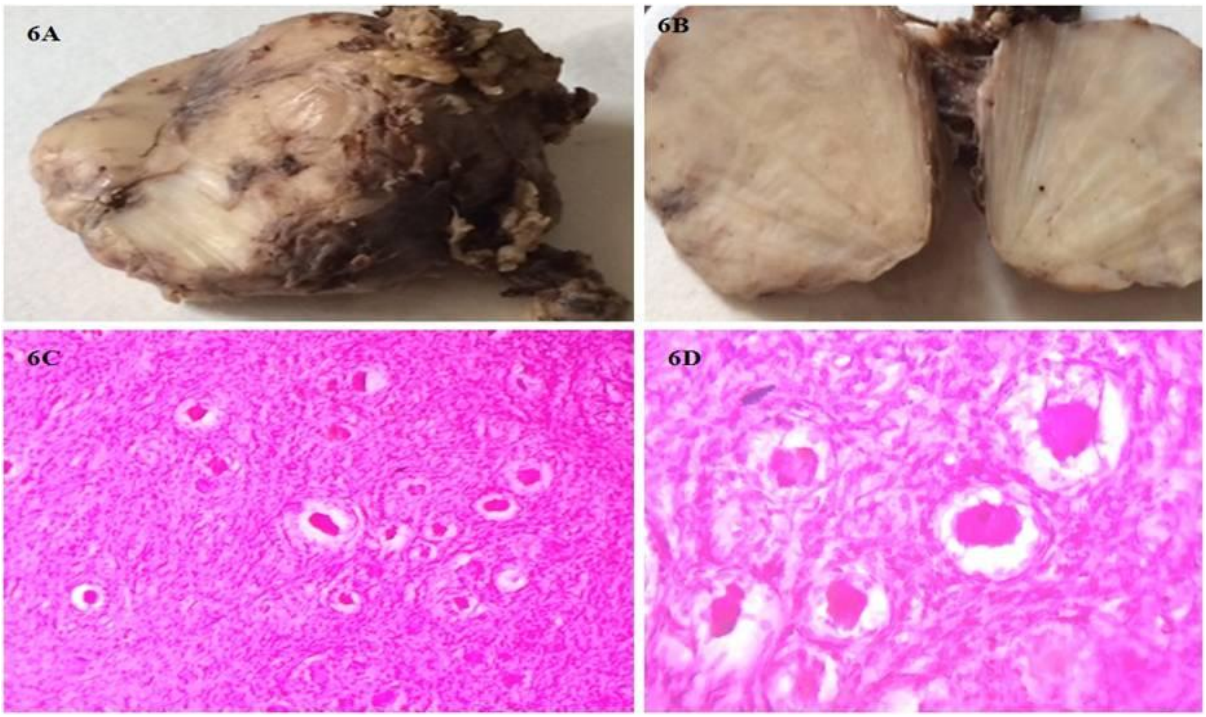


Figure - 6A: Gross of ganglioneuroma, solid and firm in consistency.
Figure - 6B: C/S: Solid homogenous grey white areas with mucoid glistening appearance.
Figures - 6C, and 6D: H and E on 10X, 40X views respectively showing benign neuromatous tumor interspersed by large ganglion cells.



An adrenal gland tumor is a benign or malignant neoplasm which has varied presentations and distinct clinical features, specific for each neoplasm. Prompt diagnosis and treatment of these tumors is essential as these tumors are active hormone secretors and have a grave clinical course.

Primary adrenal tumors are comparatively rare in literature. The exact statistics of the present scenario are unavailable. Few researchers have found that about 200 to 500 adults are diagnosed with adrenocortical cancer in United States each year. However the definite statistics for adrenal tumors worldwide is not available.

Several studies have shown that adrenal tumors are incidental findings. Patients have attended clinics for an unrelated medical condition and imaging has identified the suprarenal mass. George, et al., in their study have mentioned that 1-5% of the adrenal tumors were incidental findings. Autopsy prevalence for these tumors was 2-9% and the most important silent adrenal tumor was pheochromocytoma [1]. In another study by David Arnaol, et al., the incidence of adrenal masses found on abdominal CT scans was between 0.6% and 1.3% whereas the incidence of these masses on all CT scans, including thoracic, abdominal, and pelvic, was between 0.4% and 4% [2]. In the present study, 3 out of 8 cases were incidentally detected which is comparable with the literature. However this calls for an extensive research into the incidence of adrenal tumors in the population of Telangana. Also there is no literature available regarding the mean age incidence and male to female ratio of occurrence of adrenal tumors to the best of our knowledge. Few websites have mentioned a mean age of 44 years. In our study group mean age was 36 years.

Differential diagnosis of adrenal mass comprises of various neoplastic and non-Neoplastic conditions. Non neoplastic conditions include hyperplasia, cysts, hemorrhage into the gland and tuberculosis. Benign tumors include adenoma, myelolipoma, lipoma, ganglioneuroma, pheochromocytoma and malignant tumors include adrenal carcinoma, malignant pheochromocytoma and metastatic tumors [3]. The most difficult adrenal masses to diagnose are adrenal cancers and metastatic cancers because they can often mimic adenomas morphologically, as solitary mass lesion. In the present study we encountered only neoplastic lesions.

According to the available statistics, pheochromocytoma is present in 0.1% to 1% of patients with hypertension. The incidence of pheochromocytoma is 2 to 8 per million persons per year. In the present study, we had 4 cases of pheochromocytoma of which only one case was incidentally detected. 2 had hypertension and other one presented with catastrophic acute abdominal emergency with bleeding. Manger, et al. in their study found that 50% of the pheochromocytomas are detected at autopsy [4]. Cohen DL, et al. in their study have shown that a good number of patients with histologically diagnosed pheochromocytomas, were lacking clinical symptoms [5].

Secondary changes have been rarely reported in pheochromocytoma. Differential diagnosis to be considered for a black adrenal mass are as follows: Spontaneous hemorrhage into adrenal gland and forming a mass lesion, pseudopheochromocytoma, hemorrhage into adrenal tumors, either pheochromocytoma or adrenal adenoma, pigmented neoplasm of adrenal gland like pigmented/black pheochromocytoma, pigmented adrenal adenoma, metastatic melanoma or rarely primary malignant melanoma of adrenal gland. Thus special stains and IHC have a great role to play in discriminating one from another. In our study, we had a case of pheochromocytoma which was intensely black on gross examination and on H and E looked like a pigmented pheochromocytoma. The pigment, on close examination was found to be overlaying the section and was not found intracytoplasmically. Associated collections of xanthoma cells/ macrophages, in conjunction with positive perl's stain and negative bleaching, supported by

positive synaptophysin, S-100 in the sustentacular cells, negative HMB 45, led to the diagnosis of hemorrhage into adrenal gland tumour - Pheochromocytoma. We considered this as a diagnostic pitfall of routine H and E where there is some chance of misinterpreting pigments. This is where special stains and IHC play a pivotal role in confirming the nature of the pigment. It is important to identify the nature of the pigment, as melanomas carry a poor prognosis. Hemorrhages into adrenal masses are uncommon but a few of them have been reported in the literature. Marti JM, et al. in their study have concluded that whenever there is a hemorrhage into an adrenal mass the first possibility will be an neoplasm and hemorrhages are more common in pheochromocytoma compared to other adrenal neoplasms [6]. Even in our study we came across hemorrhage only in pheochromocytoma. Treatment for these hemorrhages will be blood transfusion or embolization if severe.

Adrenal adenoma is the most common benign neoplasm of adrenal gland. These tumors can be functional by secreting hormones. Julie H song et al., have quoted that 75% of the adrenal masses were Adrenal Adenoma [7]. But in our study we had only two cases which is about 25%. This discrepancy could be due to low sample size of our study. In the present study one of the cases which was diagnosed as adrenal adenoma, was a 19 year old female who presented with primary amenorrhoea and virilization. The hormonal assays of this patient showed elevated testosterone {350 ng/dl, (normal 5-90)} and also elevated deyhydroepiandrosterone-sulfate (DHEA-S, 540 microg/dl). Forsbach G, et al. have reported a case of adrenal adenoma associated with adrenal hyperplasia [8]. Other adrenal adenoma encountered in our study was having atypical features with hyper chromatic nuclei, bizarre giant cells and mitoses. The modified Weiss criteria and IHC was applied and proved that the tumour was an adenoma with atypical features and not a carcinoma.

Modified Weiss criteria is as follows:

- High nuclear grade (III or IV based on Fuhrman criteria),
- Mitotic rate >5/50 HPF,
- Atypical mitotic figures,
- Presence of <25% of clear, vacuolated cells,
- Diffuse architecture >1/3 of tumor formed pattern less sheets of cells,
- Necrosis,
- Venous invasion,
- Sinusoidal invasion,
- Capsular invasion

(Each criterion is scored 0 when absent and 1 when present in the tumor. Score of $\geq$ 3 is malignant)

Myelolipoma of adrenal gland is relatively a rare tumor with extra medullary hematopoiesis. Extra medullary hematopoiesis is a compensatory mechanism secondary to anemia as a result of hemolysis or bone marrow failure. Most common sites for extra medullary hematopoiesis are liver and spleen but it has also been reported in adrenal glands, breast, duramater and bowel [9, 10, 11, 12].

Banerji JS, et al., has reported a case of extra medullary hematopoiesis in adrenal gland which was an incidental finding [13]. In our study, 1 case of myelolipoma of adrenal gland was detected incidentally while evaluating the patient for an unrelated medical condition. The patient was a 55 year old female complaining of weakness. Routine complete blood counts were reviewed for this patient after the diagnosis on histopathology. Her hemoglobin was 10.5 gms%, total white blood cell counts, differential count and platelet counts were within normal limits. No abnormality was noted in the morphology of red blood cells. Urine was normal.

Ganglioneuroma was another incidentaloma, having well encapsulated gross and homogenous, firm grey white texture on cut section. Histopathology revealed spindle cell proliferation arranged in short fascicles having

serpentine nature, interspersed by large ganglion cells with abundant cytoplasm, eccentric nucleus having prominent eosinophilic nucleolus. Fine, sparse nissl granules are noted in the cytoplasm. No features of nuclear pleomorphism, mitoses or necrosis noted. As histopathology clinched the diagnosis, IHC was not done. These tumours can also exist as composite tumors, in association with pheochromocytoma.

The best criteria for categorizing a tumor as malignant, especially in endocrine tumors are metastasis and bilaterality, as pleomorphism, atypia and mitosis have no significance. Statistically significant correlations between p53 or Ki67 and the occurrence of metastases in adrenocortical carcinoma and malignant pheochromocytoma were not found in the literature. Thus all cases underwent whole body scanning to rule out metastasis in all the 6 cases (excluding myelolipoma and ganglioneuroma).

Immunohistochemistry plays an important role in diagnosis of adrenal masses, delineating primary from secondary tumours, cortical from medullary tumours and lastly benign and malignant tumours in adrenal cortical tumours. As adrenal tumours have a varied morphology, many differentials have to be considered before a final diagnosis is offered, especially when they are non-functioning and asymptomatic. Differentials to be entertained are common metastatic tumours, especially from lung which have propensity to harbor in adrenal glands, and renal tumors, due to their close proximity to adrenal glands, as they can also mimick adrenal tumors, morphologically.

Conclusion

We encountered a total of 8 cases of Adrenal gland tumors, including almost one from each category of the WHO classification. Majority of the tumours were seen in the age group of 20-40 years with female preponderance. Pheochromocytoma was the commonest tumor encountered (50%). Adrenal tumors are rare, can be incidental, may be functional or non functional and need multi-disciplinary approach to arrive at a diagnosis, including clinical, radiological, surgical, histopathological, supplemented by special and IHC stains. All the cases were sporadic in origin, occurring in adults, as other endocrine organs did not reveal any mass lesions radiologically, clinically, biochemically, ruling out the possibility of associated MEN syndromes. To the best of our knowledge all the cases are doing well, after surgical excision.

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